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Systemic Manifestations of Erythema Nodosum

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• **The systemic manifestations accompanying erythema nodosum can be differentiated from those associated with the precipitating infectious process and from coincident disease processes.**

Erythema nodosum itself is characterized by (a) skin lesions at pressure sites, (b) malaise, fever and occasionally chills, (c) arthritis (70 per cent) and (d) over-reactivity of tissue. Tissue hypersensitivity is most pronounced at sites of trauma, at sites of specific skin testing, and in the lymphoid system draining infections in the pharynx and lung.

Common infections of the respiratory tract most often antedate attacks of erythema nodosum. In New England, a β-hemolytic streptococcus infection is a common causative factor, and tuberculosis is an unusual causative factor. In endemic areas, coccidioidomycosis is a common cause of erythema nodosum.

The most important coincidental disease process is rheumatic heart disease. Rarely is it a sequel of erythema nodosum. Other "collagen diseases" may coexist with erythema nodosum.

Erythema nodosum is its own most common complication. Follow-up studies indicate that over half of the patients have a subsequent attack, and a certain number have recurrent episodes for months to years.

The management of erythema nodosum is expectant. In each case the cause should be found and treated. Steroid treatment is rarely justified, and should be used only after tuberculosis and other treatable entities have been ruled out.

THE COMMON benign form of erythema nodosum is characterized by tender, bruise-like lesions on the shins of a patient who is ambulatory. Much of the knowledge of erythema nodosum, however, has come from studies on the more severe and less frequent variety of this disease which is marked by systemic symptoms and a protracted course. The purpose of this presentation, which is based on observation and review of the records of 163 patients with the disease, is to differentiate the clinical manifestations of erythema nodosum itself from those arising from coincident or causative underlying processes.

The clinical material used in this study was seen in the medical clinics of the Peter Bent Brigham Hospital, Boston, Massachusetts, and in the author's practice in Boston and in Palo Alto, California.

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DIAGNOSIS OF ERYTHEMA NODOSUM

The more severe type of erythema nodosum[5] is a systemic disorder accompanied by tender, sometimes spontaneously painful, indurated lesions of the skin and subcutaneous tissues. The diagnosis cannot be made from its systemic symptoms, however, without the presence of these lesions somewhere on the cutaneous surfaces of the body. Usually, bilateral lesions resembling bruises are found on the shins.

Sometimes these are entirely subcutaneous, or are in bizarre locations, such as over the vulnerable pressure prominences of the ankles, knees and elbows, or even on the face and neck. Early lesions may be superficial, hive-like, nonpruritic, erythematous plaques which later become unmistakable erythema nodosum lesions.

Characteristically, nodes occur in successive crops. Usually individual nodes start as indurated subcutaneous nodules which, in the course of one to two days, enlarge to a diameter of 1 to 4 cm. and involve the overlying skin in edema, erythema and, at times, a mild degree of ecchymosis. As they subside during the succeeding days to a week or longer, a fine overlying paper-like scale may develop. Occasionally, frank purpura of the nonthrombocytopenic variety appears either in separate lesions or as a part of erythema nodosum lesions. At the height of the disease, lesions may become confluent, particularly on the parts of the legs that rest against each other during sleep. At this stage of the disease, the most ordinary minor trauma to bony prominences, or even to the soft tissues of the body, may be followed within one to two days by typical lesions. Following recovery, this vulnerability to pressure disappears.

Some difficulties in diagnosis and interpretation have arisen when indurated lesions are persistent. Most often, erythema nodosum is readily distinguished from other nodular processes such as nodular vasculitis, erythema induratum, Schoenlein's purpura and Weber-Christian's syndrome, which also may accompany erythema nodosum. In doubtful cases, biopsy is helpful; but it is not the final court of appeal, since erythema nodosum is a clinical and not a pathological entity.

TABLE 1.—*Record of Preexisting or Subsequent Diseases in 90 Patients*

	No. Patients
Preexisting rheumatic heart disease	11
Subsequent rheumatic heart disease	1
Recurrent erythema nodosum	9
Preceding or subsequent erythema nodosum	57

Duration of follow-up was one year in 13 cases, two to four years in 28 cases, five to 10 years in 30 cases, 10 to 20 years in 11 cases, and 20 to 30 years in 8 cases.

Usually, lesions of erythema nodosum heal without necrosis or scar formation. Lesions should not be incised as unfortunately has been done all too often. Occasionally, confluent lesions go on to ulceration, not only in persons with ulcerative colitis[2] but also in persons who have no bowel disorder and no apparent overt causative infectious process.* Rarely, a drug is found to be the cause of erythema nodosum.[11] Discovering and discontinuing such an agent is just as important as finding and eradicating the usual infections which precipitate most attacks of erythema nodosum.

SYSTEMIC SYMPTOMS OF ERYTHEMA NODOSUM

Apart from the precipitating causes, erythema nodosum itself can be a severe illness. In addition to the skin lesions, malaise, fever and sometimes chills occur. Usually acute attacks last one to five weeks and subside without residual signs or symptoms. Approximately one patient in ten, however, has an attack that smolders on for months to a year or more†[15] (Table 1).

Arthritis: Most erythema nodosum patients in this study (70 per cent) had joint manifestation of some type associated with the acute attack (Table 2). In its mildest form, this consisted of arthralgia. In its most obvious form there was acute serous arthritis with redness, heat, swelling and pronounced pain on motion. Chart 1 shows the interval between the onset of arthritis and the development of the lesions which establish the diagnosis. In general, patients with the milder forms of the systemic disease had the worst trouble with their joints, perhaps because they remained on their feet up to the onset of more acute symptoms. Once bedridden, patients had less arthritis. Arthritis occurring late in the acute course of erythema nodosum was less common.

The joints involved most often were the ankles and knees. Arthralgia of the wrists and fingers was surprisingly common in cases in which these symptoms were asked about by the examining physician.

*Observed three times in the 163 patients of this study.

†Observed nine times in the 163 patients of this series. Data given for smoldering or subsequent erythema nodosum is weighted by the fact that the authors' special interest in this disease has resulted in special efforts of physicians and the patients themselves to refer problem illnesses for study.

TABLE 2.—*Arthritis and Erythema Nodosum*

	Records Available	Number Patients	Per Cent of Total	Rheumatic Heart Disease	
				No. Patients	Per Cent
Past history arthritis	163	39	24	4	10
Subsequent history arthritis	78	18	23	3	17
Arthritis with erythema nodosum	137	96	70	9	9.4
No arthritis with erythema nodosum	137	40	30	4	10
Rheumatic heart disease present, all patients	163	....	....	15*	9.2

*Includes two patients with new rheumatic heart disease with or after erythema nodosum.

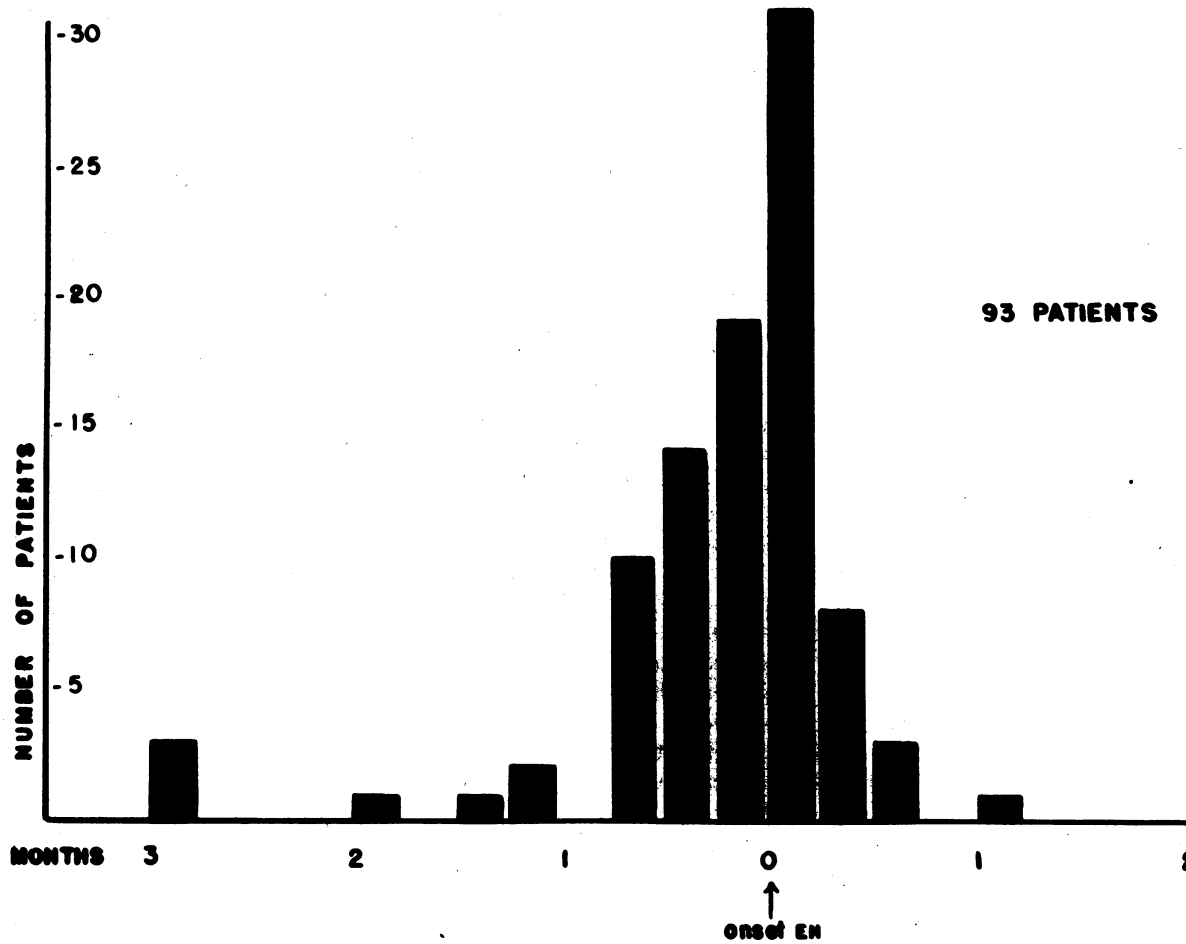

Chart 1.—Interval between onset of arthritis and erythema nodosum.

Objective findings in the no-weight-bearing joints were unusual. Subjective back pain occurred occasionally.

Poncet's arthritis: In 1902, Poncet[13] described a transient aseptic type of arthritis in patients with tuberculosis which he thought was related to the tuberculous process. Erythema nodosum due to tuberculosis should be an ideal circumstance in which to study this entity. In the present study there were five patients who were proven by the isolation of tubercle bacilli to have active tuberculosis (Table 3). None of the five had arthralgia or arthritis with an episode of associated erythema nodosum. In one of these subgroups of patients, a subsequent attack of erythema nodosum a year later associated with an upper respiratory tract infection was accompanied by mild arthralgia. At that time, studies revealed evidence of a streptococcal and not a tuberculous infection. It is of interest that erythema nodosum ordinarily is associated with arthralgia and arthritis, and yet in all these cases of proven tuberculosis the patients were free of joint symptoms at the time of a known tuberculous infection.

Lungs: Many observers[5,10,14] have noted pulmonary abnormalities associated with erythema nodosum. Patients with these changes have a mild to severe harassing dry cough (Table 4). The most characteristic pulmonary finding is hilar adenopathy, with or without increased lung marking or mottling of the lungs. A perihilar clear zone separating the node from the mediastinum structures (Figure 1) has been noted often enough in this

TABLE 3.—*Tuberculosis and Erythema Nodosum*

	Records Available	Tuberculosis	
		No. Patients	Per Cent
Family history tuberculosis	163	12	7.3
Past history clinical tuberculosis	163	7	4.3
Past exposure to tuberculosis	163	4	2.4
Proven tuberculosis with erythema nodosum	163	5	3.0
Tuberculin tests (purified protein derivatives)	53	....	....
First strength positive	9		
Second strength positive	13		
Second strength negative	31		

TABLE 4.—*Roentgenologic Findings in the Chest in 93 Patients with Erythema Nodosum*

		No. Cases
Entirely negative		57
Increased root markings		10
Enlarged lymph nodes		12
Enlarged lymph nodes with mottling in the lung fields		6
Mottling of the lungs		2
Apical infiltrations		5
Inactive tuberculosis	4	
Active tuberculosis	1	
Total		93

disease and not in other conditions, to suggest that this is a presumptive diagnostic finding. In none of the patients in the present series were these pulmonary patterns found to be due to tuberculosis. Of parenchymal lesions found in the upper lung fields only, four were inactive and one was active apical tuberculosis.

The changes in peripheral lung fields that have been seen by the author, clear within one to three weeks. Hilar nodes may persist for one to four months. In some series of patients, one or another of these pulmonary patterns has been found to be due to a recognizable infection which itself is the cause of the erythema nodosum. In the Scandinavian countries where tuberculosis is still prevalent, tubercle bacilli have been obtained from the sputum or gastric washing in a number of these persons. In the San Joaquin Valley in California, evidence of a concurrent coccidioidomycosis infection is a common finding. In New England, benign bronchitis is the most commonly recognized cause of pulmonary findings.

Pulmonary changes seem to be, in part, a manifestation of erythema nodosum itself. The peripheral infiltrations of the lung fields undoubtedly represent a local infection and the hilar nodes represent a secondary regional adenitis. The most interesting feature of these changes is the relatively mild degree of bronchitis or pneumonitis which brings about the central adenitis and systemic symptoms. In the same way, simple tonsillitis may be accompanied by a more obvious satellite cervical adenitis, the two changes together precipitating striking systemic manifestations. These effects seem to be a part of a general tissue over-reactivity which contributes to skin and joint changes as well. Tuberculin tests[3] or streptococcus skin tests[4] during the active phase of the disease will also provoke clinical exacerbations, whereas they do not do so at other times in these patients.

Laboratory findings: Transient, slight albuminuria may occur at the height of an attack. Where acute infection does not complicate erythema nodosum, the changes in the blood are minimal. In some patients with high fever and a protracted course, mild anemia develops. The number of leukocytes may be elevated—from 12,000 to 25,000 in a severely ill patient—with a shift to the younger forms. Normal or low leukocyte counts may be seen where there is an accompanying virus infection. The sedimentation rate may be elevated, depending on the intensity of the disease.

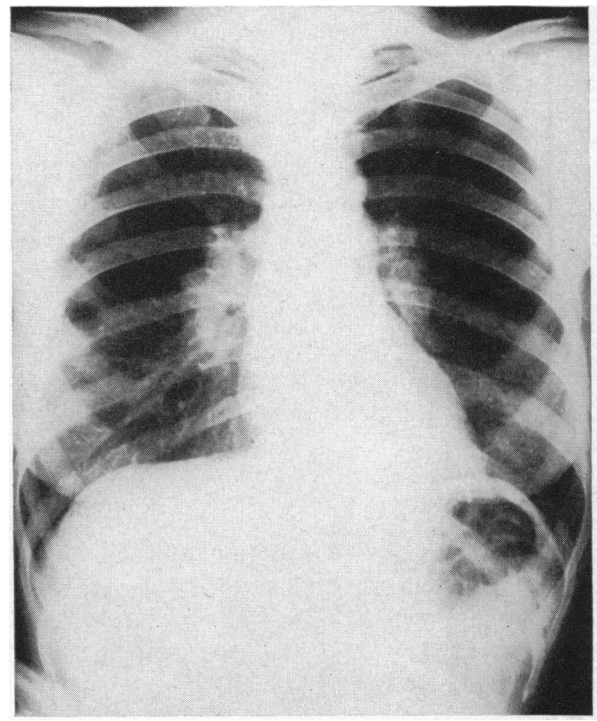

Figure 1.—Hilar adenopathy associated with erythema nodosum.

Total proteins: Total serum proteins are usually within the normal range. Occasionally an elevated globulin value is encountered much as in other systemic disorders that run a protracted course.

Electrocardiograms: Erythema nodosum does not cause alterations in the electrocardiographic tracings.

Bacteriology: In this study (Table 5) β-hemolytic streptococci were recovered from the pharynx in 20 of 48 cases in which cultures were made one or more times, and once from the antrum, once from a retained tooth fragment, and once from a tooth socket after dental extraction for an abscessed tooth. In the last three instances, throat cultures contained no β-hemolytic streptococci. No β-hemolytic streptococci were recovered from eight additional patients who had received an antibiotic just prior to study. The importance of the β-hemolytic streptococci in the northeast part of the United States where this study was done is abundantly apparent.

TABLE 5.—*Beta-Hemolytic Streptococci Associated with Erythema Nodosum*

		No. Patients
Beta-hemolytic streptococci recovered		23
Pharynx	20	
Antrum	1	
Retained tooth fragment	1	
Tooth socket	1	
	23	
No Beta-hemolytic streptococci recovered:		
Pharynx		25
Skin tests with Beta-hemolytic streptococcus vaccine:		
Positive		59
Negative		3

TABLE 6.—*Relationship of Coincidence of Rheumatic Heart Disease and Erythema Nodosum to Family History of Rheumatic Fever*

	No. of Records Available	No. of Patients	Per Cent
Family history of rheumatic fever*:			
Patients with preexisting rheumatic heart disease	11	4	36.0
Patients with no rheumatic heart disease	152	10	1.5
Carditis with erythema nodosum	163	1	0.6

*Rheumatic fever = Rheumatic heart disease, six patients; chorea, one patient; acute rheumatic fever, one patient.

Skin tests: Emphasis on tuberculosis as a cause of erythema nodosum has resulted in a considerable body of uncritical misinformation on this subject. Table 3 gives the results of tuberculin tests on a group of patients with the more severe forms of erythema nodosum. It is seen that positive reaction to tuberculin tests is not the rule.

Beta-hemolytic streptococcus skin tests (Table 5) may even precipitate new crops of erythema nodosum[5] just as tuberculin skin tests have been reported to do in the past.[4] This occurred in 7 of 59 patients with positive streptococcus reactions and did not occur where other skin tests were done. It did not occur in association with tuberculin testing. Skin tests have been of value in one other respect: The lack of anergy in patients with erythema nodosum is looked upon by the author as evidence that erythema nodosum is unrelated to sarcoid. Contrary claims by other investigators[8] have not been substantiated in the present series or other large series of reported cases.[15,9]

Rheumatic fever: The common occurrence of joint manifestation in erythema nodosum has led to much confusion in the relation between rheumatic fever and erythema nodosum. The frequent presence of a streptococcus infection antedating erythema nodosum has added to this confusion.[16,6,12] Furthermore, it is known that a certain number of persons in whom erythema nodosum develops also have rheumatic heart disease. Table 6 shows the incidence of rheumatic heart disease in a group of patients with erythema nodosum. The coincidence of erythema nodosum and rheumatic heart disease is greater than that expected in a random sampling of the population. To an extent, this might be expected in a region where a streptococcus as an etiologic factor is common.

When a family history of rheumatic heart disease is carefully sought, it is found (Table 6) that patients with erythema nodosum alone have the expected low incidence of rheumatic heart disease history and that those with both erythema nodosum and rheumatic heart disease have the expected high incidence of a family history of rheumatic heart disease. In only one patient in the series did rheumatic heart disease develop subsequent to erythema nodosum and in one patient acute carditis developed coincident with erythema nodosum (Table 6). All the other patients with erythema nodosum and rheumatic heart disease were known to have heart disease before the first attack of erythema nodosum.

This situation may be summarized by saying that both erythema nodosum and rheumatic heart disease can appear in the same person who has the hereditary background of susceptibility. Rarely do they appear simultaneously. Unlike rheumatic fever, which is initiated by β-hemolytic streptococcus infection only, erythema nodosum may be set off by many infectious processes.

Follow-up examination: Table 1 gives data on follow-up studies. Combining this data with data on a past history of other attacks of erythema nodosum, it is found that, of 90 patients followed for a year or longer, 57 had more than one episode and 9 unfortunately had a chronic relapsing form of erythema nodosum.

The best single clue to the relation between erythema nodosum and rheumatic heart disease is to be found in follow-up studies. In persons (65 per cent) with joint pains and fever who develop proved rheumatic heart disease, murmurs and evidence of cardiac involvement will develop usually within one year,[7] and almost always within five years.[1] Only one patient in the present series who did not have rheumatic heart disease at the time of erythema nodosum developed subsequent rheumatic heart disease.

Subsequent roentgenological examinations of the chest (Table 1) gave no further evidence of tuberculosis as the cause of erythema nodosum in patients not known to have tuberculosis at the time erythema nodosum developed.

Treatment of erythema nodosum with systemic manifestations: Many patients with erythema no-

dosum will recover without event if given only bed rest and symptomatic therapy. This management is recommended as the standard form of treatment.

During this treatment, diligent efforts should be made to determine the infectious or the chemical allergen causing the disease. The only specific treatment for erythema nodosum is specific removal of such a cause.

The most important etiologic factor to rule out is tuberculosis. When found, it should be treated according to accepted principles and the erythema nodosum treated with appropriate symptomatic management.

When evidence of a β-hemolytic streptococcus infection is found, penicillin should be given parenterally for from ten days to two weeks. This will not alter the speed of normal recovery but may be helpful in shortening a protracted course of erythema nodosum.

When there is evidence that an infected tooth or infected tonsils are at fault, antibiotic therapy alone is not enough. The infected focus should be removed surgically after a period of antibiotic treatment. Erythema nodosum complicating ulcerative colitis or regional ileitis may improve on antibiotic, dietary, and other treatment. When it does not, it is ominous and portends the need for surgical resection.

Only rarely will there be occasion to use cortisone derivatives or corticotropin (ACTH) for excruciatingly painful smoldering erythema nodosum or for long-standing erythema nodosum which is causing so much arthritis that the patient cannot remain gainfully employed. This treatment should be reserved for patients in whom tuberculosis is not a cause and for those on whom careful observation has shown that a specific treatment for a known cause cannot be used instead.

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REFERENCES

1. Boone, J. A., and Levin, S. A.: The prognosis in "potential rheumatic heart disease" and "rheumatic mitral insufficiency," Am. J. Med. Sci., 195:764-770, June 1938.

2. Brooke, P. A.: Erythema nodosum-like lesions in chronic ulcerative colitis, N. E. Med. J., 209:233-235, Aug. 3, 1933.

3. Chauffard, A., and Troisier, J.: Erytheme noueux experimentale par injection intradermique de tuberculine, Bull. med. Paris, 27:7, 1909.

4. Collis, W. R. F.: A new conception of the aetiology of erythema nodosum, Quart. J. Med., 1:141-156, Jan. 1932.

5. Favour, C. B., and Sosman, M. C.: Erythema nodosum, Arch. Int. Med., 80:435-453, Oct. 1947.

6. Goldstein, H. I.: Erythema multiforme and erythema nodosum with streptococci sore throat, M. J. and Rec. 134: 266-267, Sept. 16, 1931.

7. Jones, T. D., and Bland, E. F.: Clinical significance of chorea as a manifestation of rheumatic fever; a study in prognosis, J. Amer. Med. Assoc. 105:571-577, Aug. 24, 1935.

8. Kerley, P.: The significance of the radiological manifestations of erythema nodosum, Brit. J. Radiol., 15:155-165, June 1942.

9. Lofgren, S.: Erythema nodosum; studies on etiology and pathogenesis in 185 adult cases, Acta Med. Scand., 124: Suppl. 174, pp. 1-197, 1946.

10. Paul, L. W., and Pohle, E. A.: Mediastinal and pulmonary changes in erythema nodosum, Radiology, 37:131-137, Aug. 1941.

11. Perrin, L.: Un cas d'erytheme noueux du a l'iodure de potassium, Marseille-med., 29:567, 1892.

12. Pilot, I.: Focal infection and erythema nodosum, J. Amer. Med. Assoc., 101:2145, Dec. 30, 1933.

13. Poncet, A.: Rheumatisme tuberculaire abarticulaire; localizations viscerales et autres du rheumatisme tuberculaire, Lyon med., 99:65-82, July 1902.

14. Rotnes, P. L.: Untersuchungen ueber Erythema Nodosum in erwachsenen Alter, Acta dermat., venerol., 17: Suppl. 3, 1-226, 1936.

15. Spink, W. W.: Pathogenesis of erythema nodosum, with special reference to tuberculosis, streptococcic infection, and rheumatic fever, Arch. Int. Med., 59:65-81, Jan. 1937.

16. Stone, W. R.: Erythema nodosum associated with streptococcic faucitis, New York Med. J., 118:673-674, Dec. 1923.